PA NT COOPERATION TREAT)

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 16 May 2000 (16.05.00)	
International application No. PCT/EP99/07764	**Applicant's or agent's file reference** RE/DM/B45158
International filing date (day/month/year) 08 October 1999 (08.10.99)	**Priority date** (day/month/year) 16 October 1998 (16.10.98)
Applicant GARCON, Nathalie	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 April 2000 (15.04.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO **34, chemin des Colombettes** **1211 Geneva 20, Switzerland**	Authorized officer S. Mafla
Facsimile No.: (41-22) 740.14.35	Telephone No.: (41-22) 338.83.38

Form PCT/IB/331 (July 1992)

EP9907764

PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 39/39, 39/00, 39/29, 39/015, A61P 31/12, 31/04, 33/06, 35/00, 37/08

A3

(11) International Publication Number: WO 00/23105

(43) International Publication Date: 27 April 2000 (27.04.00)

(21) International Application Number: PCT/EP99/07764

(22) International Filing Date: 8 October 1999 (08.10.99)

(30) Priority Data:

9822703.6	16 October 1998 (16.10.98)	GB
9822709.3	16 October 1998 (16.10.98)	GB
9822712.7	16 October 1998 (16.10.98)	GB

(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM BIOLOGICALS S.A. [BE/BE]; Rue de l'Institut 89, B–1330 Rixensart (BE).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: GARCON, Nathalie [FR/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B–1330 Rixensart (BE).

(74) Agent: DALTON, Marcus, Jonathan, William; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(88) Date of publication of the international search report:
3 August 2000 (03.08.00)

(54) Title: ADJUVANT SYSTEMS AND VACCINES

(57) Abstract

The present invention provides vaccine and adjuvant formulation comprising an immunostimulant and a metal salt. The immunostimulant is adsorbed onto a particle of metal salt and the resulting particle is essentially devoid of antigen.

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EE	Estonia	**LR**	Liberia	**SG**	Singapore		

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/07764

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K39/39 A61K39/00 A61K39/29 A61K39/015 A61P31/12
A61P31/04 A61P33/06 A61P35/00 A61P37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
BIOSIS EPO-Internal PAJ WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 00697 A (SMITHKLINE BEECHAM BIOLOGICALS) 9 January 1997 (1997-01-09) the whole document	1-28
A	WO 96 26741 A (SMITHKLINE BEECHAM BIOLOGICALS) 6 September 1996 (1996-09-06) the whole document	1-28
A	WO 98 15287 A (SMITHKLINE BEECHAM BIOLOGICALS) 16 April 1998 (1998-04-16) the whole document	1-28
A	EP 0 812 593 A (SMITHKLINE BEECHAM BIOLOGICALS) 17 December 1997 (1997-12-17) the whole document	1-28

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 May 2000	29/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Moreau, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/EP 99/07764

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 99 48525 A (SMITHKLINE BEECHAM BIOLOGICALS) 30 September 1999 (1999-09-30) the whole document	1-28

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/07764

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 27 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

information on patent family members

Inter ional Application No
PCT/EP 99/07764

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9700697 A	09-01-1997	AU	695720 B	20-08-1998
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		AU	696338 B	10-09-1998
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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter nal Application No
PCT/EP 99/07764

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 812593 A		AU 705739 B	03-06-1999
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		DK 689454 T	08-12-1997
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		NO 953759 A	22-09-1995
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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
A61K 39/39, 39/00, 39/29, 39/015, A61P 31/12, 31/04, 33/06, 35/00, 37/08

A2

(11) International Publication Number: WO 00/23105

(43) International Publication Date: 27 April 2000 (27.04.00)

(21) International Application Number: PCT/EP99/07764

(22) International Filing Date: 8 October 1999 (08.10.99)

(30) Priority Data:

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(75) Inventor/Applicant *(for US only)*: GARCON, Nathalie [FR/BE]; SmithKline Beecham Biologicals S.A., Rue de l'Institut 89, B–1330 Rixensart (BE).

(74) Agent: DALTON, Marcus, Jonathan, William; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published

Without international search report and to be republished upon receipt of that report.

(54) Title: ADJUVANT SYSTEMS AND VACCINES

(57) Abstract

The present invention provides vaccine and adjuvant formulation comprising an immunostimulant and a metal salt. The immunostimulant is adsorbed onto a particle of metal salt and the resulting particle is essentially devoid of antigen.

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
RE/B45158		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/07764	08/10/1999	16/10/1998
International Patent Classification (IPC) or national classification and IPC A61K39/39		
Applicant SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 11 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☒ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/04/2000	04.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Thumb, W Telephone No. +49 89 2399 7350

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07764

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-26	as originally filed	

Claims, No.:

1-26,28-31	with telefax of	16/10/2000

Drawings, sheets:

1/6-6/6	as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   ☐ the language of publication of the international application (under Rule 48.3(b)).
   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.
   ☐ filed together with the international application in computer readable form.
   ☐ furnished subsequently to this Authority in written form.
   ☐ furnished subsequently to this Authority in computer readable form.
   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:
   ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application.

   ☒ claims Nos. 28-30.

because:

   ☒ the said international application, or the said claims Nos. 28-30 relate to the following subject matter which does not require an international preliminary examination (*specify*):
   see separate sheet

   ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos. .

2. A meaningful international preliminary examination report cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the standard.

   ☐ the computer readable form has not been furnished or does not comply with the standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

   Novelty (N) Yes: Claims 1-26, 28-31

	No:	Claims	
Inventive step (IS)	Yes:	Claims	7-26, 28-31
	No:	Claims	1-6
Industrial applicability (IA)	Yes:	Claims	1-26, 31
	No:	Claims	

2. Citations and explanations
see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:
see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 28-30 relate to methods of treatment of the human or animal body, and are therefore considered by this Authority to be covered by the provisions of Rule 67.1(v) PCT. Consequently, no opinion well be formulated with respect of the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. The amended claims received with the telefax from 20.10.2000 do not introduce subject-matter which extends beyond the content of the application as originally filed and therefore meet the requirements of Article 19(2) PCT.

2. Reference is made to the following documents:

   D1: WO-A-98/15287
   D2: WO-A-96/26741

3. Novelty

3.1 Independent claim 1 and dependent claims 2-7 are formally novel (see comment item VIII, point 4. below), since an adjuvant composition comprising an immunostimulant adsorbed onto a metallic salt particle, said salt particle being substantially free of other antigen, and the immunostimulant not being a saponin derived from the bark of Quillaja Saponaria Molina, is not disclosed in the state of the art known to the examining authority.

3.3 Independent claim 8 and dependent claims 9-10 are novel in the sense of Article 33(2) PCT, since a process for manufacture of a vaccine composition comprising admixing an immunostimulant adsorbed to a metallic salt particle, the latter being

substantially free of antigen, with an antigen is not disclosed in the state of the art known to the examining authority.

3.4 Claims 11 and 12, referring to a vaccine composition comprising an adjuvant composition according to claims 1-7, and a vaccine produced according to the process of any of claims 8-10, respectively, are considered as being novel in the sense of Article 33(2) PCT, since said vaccine compositions do not form part of the known state of the art.

3.5 The same applies to the subject-matter of independent claim 13 and dependent claim 14 which are hence considered as being novel (Article 33(2) PCT), referring to a vaccine composition comprising metallic particles having a immunostimulant and no other antigen bound thereto.

3.6 Independent claims 15 and 16 as well as dependent claims 17-26 are also novel (Article 33(2) PCT) since a vaccine composition comprising an immunostimulant and an antigen, wherein both components are adsorbed to separate metallic salt particles, is not disclosed known in the state of the art.

3.7 The same applies to independent claims 28, 29, 30 and 31, referring to the use of the vaccine composition of novel claim 24 for the manufacture of immunotherapeutics, a method of treating a mammal using the vaccine composition of claim 24, and a kit comprising the components of claim 22, respectively. Claims 28-31 therefore meet the requirements of Article 33(2) PCT.

4. Inventive step

4.1 D1 discloses an adjuvant composition comprising liposomes, QS21 (a immunoactive molecule derived from the Quillaja Saponaria Molina tree), alum (aluminium hydroxide or aluminium phosphate), and 3-deacylated mono-phosphoryl lipid A (MPL) (Example 2, page 7, line 27- page 8, line 12). Most of the MPL is bound to the alum particles (Table on page 8). The compositions described in Example 2 do not contain additional antigen.
In addition, claim 6 of document D1 is directed towards an adjuvant composition

as described above per se.
Claim 1 differs from the teaching of D1 in that the adjuvant composition specifically excludes the use of an immunostimulant derived from the bark of Quillaja Saponaria Molina (e.g. QS21).
The underlying objective problem may therefore be seen in providing an adjuvant with different immunogen than a saponin bound to metallic particles.
However, since both QS21 and MPL are known to have an immunostimulatory effect (see also description of the instant application, page 6) and example 2 of document D1 demonstrates that both substances can be bound to metallic particles, the subject-matter of claim 1 appears to be an obvious selection among a number of known possibilities not involving an inventive activity (see also PCT Guidelines, IV-8.8(C1)(i)). Claim 1 and dependent claims 2-6, the latter referring to embodiments already disclosed in D1, therefore do not meet the requirements of Article 33(3) PCT.

4.2 The subject-matter of dependent claim 7 differs from the teaching of D1 in that CpG is used as the immunostimulant bound to a metallic particle. Even though CpG is known to possess adjuvant properties (see description of the instant application, page 6, lines 28-32), no indication can be found in the state of the art, that the CpG can be bound to a metallic particle and still retains its immunostimulant properties.
Claim 7 is therefore considered as being inventive in the sense of Article 33(3) PCT.

4.3 Document D1 discloses a process for the manufacture of a vaccine composition wherein the antigen is added to aluminium hydroxide, followed by addition of the immunostimulant MPL (Example 1, page 7, lines 15-19; page 14, lines 8-12).
The subject-matter of independent claim 8 differs from the teaching of D1 in that the order of addition of the antigen and the immunostimulant to the metallic particles is reversed.
The underlying problem may therefore be seen in providing a simplified process for the manufacture of a vaccine solution, wherein the antigen does not has to be preadsorbed to the adjuvant components, said components being metallic particles.
It is neither disclosed in nor rendered obvious from the teaching of the prior art

that it is possible to mix the immunostimulant adsorbed to metallic particles with the antigen and still obtain the desired vaccination effect. In contrast, the state of the art teaches first binding of the antigen to the particles, followed by addition of the immunostimulant (see for example D1, above, and document D2, page 7, lines 11-18).
Claim 8 and dependent claims 9 and 10 hence meet the requirements of Article 33(3) PCT.

4.4 A similar argumentation as put forward under item 4.3 above also applies to the subject-matter of claims 11-14, referring to vaccine compositions produced by the process of claims 8-10.

4.5 Independent claim 15 differs from the teaching of D1 (see item 4.1 and 4.3 above) in that the antigen, which is mixed with the adjuvant composition of claim 1, is adsorbed onto a metallic salt particle.
The underlying problem may therefore be seen in providing a vaccine solution with a defined composition consisting of an immunostimulant and an antigen being adsorbed to different particles, respectively.
Document D2 discloses a vaccine composition comprising a Herpes Simplex Virus-derived antigen adsorbed to aluminium phosphate. To this solution, the immunostimulant HPL, suspended in water, is added prior to the use of the vaccine solution (Example 1, page 7, lines 1-22).
However, it is neither disclosed nor rendered obvious in D1 or D2, that the effect of a vaccine solution can also be obtained by providing the immunostimulant and the antigen adsorbed onto separate particles. The compositions disclosed in D1 or D2 all relate to one component being present in solution, thereby most likely adsorbing to the same metallic salt particle as the respective other agent, providing for a spatial coupling of the two components.
Therefore claim 15 meets the requirements of Article 33(3) PCT.

4.6 A similar argumentation as given under item 4.5 above also applies to independent claim 16, referring to a vaccine composition comprising two complexes, an immunostimulant adsorbed to metallic salt particles, and an antigen adsorbed to different particles with no MPL adsorbed to them.
Claim 16 therefore also meets the requirements of Article 33(3) PCT.

4.7 The same applies to dependent claims 17-26, which are thus also inventive in the sense of Article 33(3) PCT.

4.8 Independent claims 28-31 referring to the use of the vaccine of claim 24 for the use in medicine, the manufacture of a therapeutic, a method of treating a mammal using the vaccine composition of claim 24, and a kit containing components of the vaccine solution of claim 22, respectively, also meet the requirements of Article 33(3) PCT following the argumentation given under item 4.5 above.

5. For the assessment of the present claims 28-30 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

6. The document WO-A-99/48525 indicated in the search report as an intermediate document is not to be regarded as state of the art according to Article 33(2) PCT, as the date of priority claimed can be allowed for the relevant parts of the present application.

Re Item VII

Certain defects in the international application

The numbering of the claims should be corrected, since the numbering does not contain a claim 27.

Re Item VIII

Certain observations on the international application

1. Even though the general concept of providing an immunostimulant and an antigen adsorbed to separate metallic salt particles is novel and inventive, the expression

"substantially" used throughout the claims is vague and open to interpretation, thereby obscuring the scope of the claims (see also PCT Guidelines, III-4.5a.) The wording should thus be amended according to the provisions of Article 6 PCT.

2. The expression "manufacture of an immunotherapeutic treatment" used claim 29 is not clear and should be amended to meet the requirements of Article 6 PCT.

3. In claim 13 it should be made clear, that by the expression "other antigen" is meant antigen which is not saponin adsorbed onto the metallic particles (Article 6 PCT).

4. Amended claim 1 excludes an immunostimulant derived from the bark of Quillaja Saponaria Molina (e.g. QuilA, QS21) being comprised in an adjuvant composition. However, in the description it is clearly stated that QuilA and its derivatives are preferred immunostimulants for use in the adjuvant composition of the present application.
Therefore, claim 1 is not supported by the description as required by the provisions of Article 6 PCT.
In addition, the attention of the applicant is drawn to the fact, that disclaiming the use of QS21 in an adjuvant composition according to claim 1 due to the anticipation of this subject-matter in document D1 will give rise to an objection because of unallowable amendments in several jurisdictions, should the application enter the national phase. For instance under the requirements of the EPC, excluding protection for part of the subject-matter of the claimed invention as covered by the application as filed is acceptable under the terms of Article 123(2) EPC only if the following conditions are met:

   (i) the subject-matter disclaimed must be precisely defined and strictly limited to the actual scope of the anticipation, and
   (ii) said anticipation must be a so called "chance anticipation", which means that it would be regarded as accidentally falling within the terms of the claims of the application in question (see e.g. T1071/97, point 3.2 and decisions cited therein).

The prior document must form part of an entirely remote and unrelated state of

the art which the skilled person, faced with the assessment of inventive step, would normally never take into consideration.
Since document D1 refers to vaccine formulations, adjuvant compositions, as well as their production and use, i.e. precisely the same technical field as the present application, the above-described conditions for validly disclaiming subject-matter are clearly not met.

Claims

1. An adjuvant composition comprising an immunostimulant adsorbed onto a metallic salt particle, characterised in that the metallic salt particle is substantially free of other antigen.

2. An adjuvant composition as claimed in claim 1, wherein the metallic salt particle is a salt of aluminium, zinc, calcium, cerium, chromium, iron, or berilium.

3. An adjuvant composition as claimed in claims 1 or 2, wherein the metallic salt is a phosphate or hydroxide.

4. An adjuvant composition as claimed in any one of claims 1 to 3, wherein the metallic salt is aluminium hydroxide or aluminium phosphate.

5. An adjuvant composition as claimed in any one of claims 1 to 4, wherein the immunostimulant is monophosphoryl lipid A.

6. An adjuvant composition as claimed in claim 5, wherein the derivative of monophosphoryl lipid A is 3-de-O-acylated monophosphoryl lipid A.

7. An adjuvant composition as claimed in any one of claims 1 to 4, wherein the immunostimulant is QS21.

8. An adjuvant composition as claimed in any one of claims 1 to 4, wherein the immunostimulant is CpG containing oligonucleotide.

9. A process for the manufacture of a vaccine composition comprising admixing the adjuvant composition described in claim 1, with antigen.

10. A process for the manufacture of a vaccine composition as claimed in claim 9, characterised in that the antigen is adsorbed onto a metallic salt particle.

11. A process as claimed in any one of claims 9 or 10, wherein the antigen is selected from the group comprising: antigens derived from Human Immunodeficiency Virus, Varicella Zoster virus, Herpes Simplex Virus type 1, Herpes Simplex virus type 2, Human cytomegalovirus, Dengue virus, Hepatitis A, B, C or E, Respiratory Syncytial virus, human papilloma virus, Influenza virus, Hib, Meningitis virus, Salmonella, Neisseria, Borrelia, Chlamydia, Bordetella, Plasmodium or Toxoplasma, IgE peptides, Der p1, pollen related antigens; or Tumor associated antigens (TMA), MAGE, BAGE, GAGE, MUC-1, Her-2 neu, LnRH(GnRH), CEA, PSA, KSA, or PRAME.

12. A vaccine composition comprising two major populations of complexes, a first complex comprising (a) an immunostimulant adsorbed onto a metallic salt particle, characterised in that said metallic salt particle is substantially free of antigen; and a second complex comprising (b) antigen adsorbed onto a metallic salt particle.

13. A vaccine composition comprising two major populations of complexes, a first complex comprising (a) an immunostimulant adsorbed onto a metallic salt particle, characterised in that said metallic salt particle is substantially free of antigen; and a second complex comprising (b) antigen adsorbed onto a metallic salt particle, characterised in that said metallic salt particle is substantially free of monophosphoryl lipid A, or derivative thereof.

14. A vaccine composition as claimed in claims 12 or 13, wherein the metallic salt present in the first and second complexes are identical.

15. A vaccine composition as claimed in any one of claims 12 to 14, wherein the second complex comprises a plurality of sub-complexes, each sub-complex comprising a different antigen adsorbed onto a metallic particle.

16. A vaccine composition as claimed in any one of claims 12 to 15, wherein the metallic salt is a salt of aluminium, zinc, calcium, cerium, chromium, iron, or berilium.

17. A vaccine composition as claimed in claim 16 wherein the metallic salt is a phosphate or hydroxide.

18. A vaccine composition as claimed in claim 17 wherein the metallic salt is aluminium hydroxide or aluminium phosphate.

19. A vaccine composition as claimed in any one of claims 12 to 18, wherein the immunostimulant is 3-de-O-acylated monophosphoryl lipid A.

20. A vaccine composition as claimed in any one of claims 12 to 18, wherein the immunostimulant is QS21.

21. A vaccine composition as claimed in any one of claims 12 to 18, wherein the immunostimulant is CpG.

22. A vaccine composition as claimed in any one of claims 12 to 21, wherein the antigen is selected from the group comprising: Human Immunodeficiency Virus, Varicella Zoster virus, Herpes Simplex Virus type 1, Herpes Simplex virus type 2,

Human cytomegalovirus, Dengue virus, Hepatitis A, B, C or E, Respiratory Syncytial virus, human papilloma virus, Influenza virus, Hib, Meningitis virus, Salmonella, Neisseria, Borrelia, Chlamydia, Bordetella, Plasmodium or Toxoplasma, stanworth decapeptide, Der p1, pollen related antigens; or cancer associated antigens, MAGE, BAGE, GAGE, MUC-1, Her-2 neu, LnRH(GnRH), CEA, PSA, tyrosinase, Survivin, KSA, or PRAME.

23. A vaccine composition as claimed in claim 22, wherein the antigen is a combination of Hepatitis A antigen and Hepatitis B antigen.

24. A vaccine composition as claimed in claim 22, wherein the plasmodium antigen is one or more antigens selected from the following group: RTS,S and TRAP.

25. A vaccine composition as claimed in claim 22 for use in medicine.

26. Use of vaccine composition as claimed in claim 22, for the manufacture of an immunotherapeutic treatment of viral, bacterial, parasitic infections, allergy, or cancer.

27. A method of treating a mammal suffering from or susceptible to a pathogenic infection, or cancer, or allergy, comprising the administration of a safe and effective amount of a vaccine composition according to claim 22.

26. A kit comprising two containers, one container having monophosphoryl lipid A, or derivative thereof, adsorbed onto a metallic salt; and the second container having antigen adsorbed onto a metallic salt.

TENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	**FOR FURTHER ACTION** see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
RE/DM/B45158		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/ 07764	08/10/1999	16/10/1998
Applicant		
SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [ ] contained in the international application in written form.

   [ ] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [ ] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of Invention is lacking** (see Box II).

4. With regard to the **title,**

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established by this Authority to read as follows:

   ADJUVANT SYSTEMS AND VACCINES

5. With regard to the **abstract,**

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No. _____

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [X] None of the figures.

INTERNATIONAL SEARCH REPORT

ernational application No.
PCT/EP 99/07764

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 27 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/07764

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K39/39 A61K39/00 A61K39/29 A61K39/015 A61P31/12
A61P31/04 A61P33/06 A61P35/00 A61P37/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS EPO-Internal PAJ WPI

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 97 00697 A (SMITHKLINE BEECHAM BIOLOGICALS) 9 January 1997 (1997-01-09) the whole document	1-28
A	WO 96 26741 A (SMITHKLINE BEECHAM BIOLOGICALS) 6 September 1996 (1996-09-06) the whole document	1-28
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A	EP 0 812 593 A (SMITHKLINE BEECHAM BIOLOGICALS) 17 December 1997 (1997-12-17) the whole document	1-28

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
22 May 2000	29/05/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Moreau, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

[redacted]tional Application No
[redacted]/EP 99/07764

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 99 48525 A (SMITHKLINE BEECHAM BIOLOGICALS) 30 September 1999 (1999-09-30) the whole document	1-28

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

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